Long-term clinical and radiographic evaluation of the effectiveness of direct pulp capping materials: A meta-analysis

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The aim of this review is to evaluate the long-term effectiveness of calcium silicate-based cement (CS) and calcium hydroxide (CH) for direct pulp capping (DPC) to human pulp-exposed permanent teeth. An electronic search and manual search were performed on 21 June 2019. Long-term clinical and radiographic evaluations of the effectiveness of CS and CH for DPC to human pulp-exposed teeth were included, and data extraction, risk-of-bias assessment and meta-analyses were performed. From 645 identified articles, 7 articles met the eligibility criteria. The meta-analyses comparing CS with CH and Biodentine with mineral trioxide aggregates (MTA) on DPC success rate were performed, and significant difference was observed between CS and CH (risk ratio=1.20; $p=0.005$), whereas no significant difference was observed between Biodentine and MTA. CS seems to be a more effective and predictable DPC material than CH; however, these analyses are based on the studies judged at high risk of bias.

Keywords: Meta-analysis, Direct pulp capping, Calcium hydroxide, Mineral trioxide aggregate

INTRODUCTION

Numbers of materials for direct pulp capping (DPC) to human teeth which has exposed dental pulp has been studied; however, lots of studies are basic research such as animal studies and *in vitro* studies, or clinical studies which do not have control group or evaluate short-term outcome. They are not adequate to evaluate long-term clinical effectiveness of DPC materials; therefore, we performed systematic review to evaluate the long-term effectiveness of DPC materials to pulp-exposed human teeth¹⁾. Previous study revealed that calcium hydroxide (CH) and calcium silicate-based cement (CS) which includes ProRoot MTA (Dentsply, Tulsa, OK, USA), white ProRoot MTA (WMTA; Dentsply), MTA-Angelus (Angelus Soluções Odontológicas, Londrina, Brazil), Endocem (Maruchi, Wonju, Korea) and Biodentine (Septodont, Saint-Maur-des-Fossés, France) were used on more than 10 randomized clinical trials (RCTs), and the range of the success rate of CS was narrower than that of CH. CS is likely to be more effective for DPC than CH. Therefore, we have following question.

Question 1: “Is CS statistically superior to CH on long-term clinical and radiographic success rate of DPC to pulp-exposed human permanent teeth?”

Moreover, previous study revealed that Biodentine was used on 3 RCTs and the success rate was remarkably

high (96.4–100%). Mineral trioxide aggregate (MTA) is a CS based on the Portland cement which contains unpurifiable mixtures of calcium silicates, calcium aluminate, calcium aluminoferrite and calcium sulfate; meanwhile, Biodentine is a CS based on high purity of calcium silicates which was synthesized to get high mechanical strength and short setting times. Therefore, we have following question.

Question 2: “Is Biodentine statistically superior to MTA on long-term clinical and radiographic success rate of DPC to pulp-exposed human permanent teeth?”

These two questions addressed according to the participants, intervention, control and outcome (PICO) principle were described in Table 1. The aim of this review is to evaluate the long-term effectiveness of CS and CH for DPC to human pulp-exposed permanent teeth by meta-analyses comparing CS with CH and Biodentine with MTA on long-term DPC success rate.

MATERIALS AND METHODS

Search strategy, study selection, data extraction and risk of bias assessment

An electronic search was performed on 21 June 2019 in 6 databases (PubMed, Google Scholar, Scopus, The Cochrane Library, ProQuest and EBSCOhost). The search terms used are mentioned in Table 2. Furthermore, the issues of the Journal of Dental Research, Journal of Endodontic, International Endodontic Journal, Journal

Color figures can be viewed in the online issue, which is available at J-STAGE.

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Table 1 PICO questions

	Question 1	Question 2
P (Participants)	pulp-exposed human permanent teeth with or without caries	pulp-exposed human permanent teeth with or without caries
I (Intervention)	DPC with CS	DPC with Biodentine
C (Control)	DPC with CH	DPC with MTA
O (Outcome)	clinical and radiographic success rate with long-term follow-up	clinical and radiographic success rate with long-term follow-up

DPC: Direct pulp capping; CS: Calcium silicate-based cement; MTA: Mineral trioxide aggregate; CH: Calcium hydroxide

Table 2 The search strategy used in PubMed (MedLine)

No.	Search terms	No. of articles
#1	“dental pulp capping” [MeSH] OR “pulp capping” [TW]	2,523
#2	“randomized” [TW] OR “randomised” [TW]	825,527
#3	#1 AND #2	192

Table 3 The eligibility criteria

Inclusion criteria	Exclusion criteria
Language: English	Not Randomized Clinical Trials
Pulp exposed permanent teeth with or without caries	Indirect pulp capping, Pulpotomy
Efficacy of pulp-capping materials	Animal studies, <i>In vitro</i> studies
Clinical and radiographic evaluation	Follow-up period: less than 6 months
Studies comparing CH with CS	Studies comparing test group with negative control group
Studies comparing Biodentine with MTA	Studies comparing the same material with different pretreatments

CH: Calcium hydroxide; CS: Calcium silicate-based cement; MTA: Mineral trioxide aggregate

of Conservative Dentistry and American Journal of Dentistry published until June 2019 (the last issue available) were manually searched.

The eligibility criteria are described in Table 3. Clinical and radiographic studies with long-term follow-up period that assessed the effectiveness of DPC materials in the treatment of human permanent teeth with exposed dental pulp with or without caries were included; moreover only randomized clinical trials (RCTs) with follow-up periods of more than 6 months were included, because RCT is a most convincing study design and a less than 3-months follow-up period would not be sufficient to guarantee the long-term prognosis of a DPC material.

The titles and abstracts of the articles were screened for a full-text evaluation, and duplicates, reviews and non-English articles were removed. The full texts were screened for eligibility, and only articles met all of the eligibility criteria were included in this study and processed for data extraction.

Data extraction and risk of bias assessment were performed as described before¹⁾. Literature search, study selection, data extraction and risk of bias assessment were independently performed by two reviewers (S.M.Z. and V.K.S.K.).

Statistical analysis

All statistical analyses were performed using Review Manager (RevMan) version 5.3.5. (Cochrane Collaboration software). Risk ratio (RR) and 95% confidence interval (CI) were used to compare the success rate of CS with that of CH and the success rate of Biodentine with that of MTA. Clinical and methodological heterogeneities among included studies were observed; therefore, combined RRs were calculated using the random effect model for meta-analysis. The Cochrane Q test and the I^2 statistic were used to test heterogeneity. Publication bias assessment were evaluated with funnel plots in RevMan 5.

Table 4 The characteristics of the included studies (part 1)

Author (year) Ref.)	Participants		Types of teeth	Deep caries	Pulp exposure size in diameter	Bleeding controlled within	Group (n) [test (T) and control (C)]	No. of operators
	No.	Age mean (range) in years						
Awawdeh <i>et al.</i> (2018) ²⁾	58	32.5 (16–51)	permanent teeth	+	NA (created with a new round bur ISO no.23)	3 min	T: Biodentine (11) C: MTA-Angelus (6)	NA
Kundzina <i>et al.</i> (2017) ⁸⁾	70	30.6 (18–55)	1st or 2nd permanent molar	+	NA	10 min	T: WMTA (33) C: CH (Dycal) (37)	6
Hilton <i>et al.</i> (2013) ⁶⁾	376	37.9 (8–90)	permanent teeth	Trauma or caries	Less than 1 mm [87.5% (MTA), 81.8% (CH)] More than 1.5 mm [12.6% (MTA), 18.3% (CH)]	until bleeding controlled or operator decided DPC not appropriate	T: ProRoot MTA (195) CH (Life) (181)	35
Parinyaprom <i>et al.</i> (2017) ⁵⁾	NA	NA (6–18)	permanent teeth	+	Less than 2.5 mm	10 min	T: Biodentine (29) C: ProRoot MTA (30)	8
Brizuela <i>et al.</i> (2017) ³⁾	169	11.3 (7–16)	permanent teeth	+	Less than 2 mm	10 min	T1: Biodentine (60) T2: WMTA (56) C: CH capsule (53)	5
Katge <i>et al.</i> (2017) ⁷⁾	50	NA (7–9)	1st permanent molar	+	Less than 1 mm	NA	T: Biodentine (29) C: MTA-Angelus (29)	1
Suhag <i>et al.</i> (2019) ⁴⁾	64	21.8 (15–40)	1st or 2nd permanent molar	+	NA	10 min	T: WMTA (32) C: CH (powder) (32)	1

CH: Calcium hydroxide; DPC: Direct pulp capping; MTA: Mineral Trioxide Aggregate; NA: not available; WMTA: white ProRoot MTA

The characteristics of the included studies (part 2)

Author (year) Ref.)	Rubber dam isolation	Disinfection or hemostasis with NaOCl	Final restoration	Final follow-up (months)	At final follow-up		Statistical analysis
					Recall rate (n/N)	Clinical and radiographic success rate (success/total) [test (T) and control (C)]	
Awawdeh <i>et al.</i> (2018) ²⁾	+	+	AM CR	36	T: 90.9% (10/11) C: 83.3% (5/6)	T: 90% (9/10) C: 100% (5/5)	No significant difference
Kundzina <i>et al.</i> (2017) ⁸⁾	±	+	CR	36	T: 93.9% (31/33) C: 91.9% (34/37)	T: 85% (NA) C: 52% (NA)	Significant difference
Hilton <i>et al.</i> (2013) ⁶⁾	±	92.3% (MTA group) 82.9% (CH group)	None (36.9%) AM (35.2%) CR (21.5%) Other (6.4%)	24	T: 93.8% (183/195) C: 96.7% (175/181)	Kaplan-Meier estimate T: 77.6%, C: 68.5% Crude success rate T: 86.3% (158/183), C: 75.4% (132/175)	Significant difference
Parinyaprom <i>et al.</i> (2017) ⁵⁾	+	+	CR (70.9%) AM (1.8%) SSC (27.3%)	18.9 ±12.9	T: 96.6% (28/29) C: 90% (27/30)	T: 96.4% (27/28) C: 92.6% (25/27)	No significant difference
Brizuela <i>et al.</i> (2017) ³⁾	+	–	CR	12	T1: 41.7% (25/60) T2: 44.6% (25/56) C: 47.2% (25/53)	T1: 100% (25/25) T2: 86.36% (19/22) C: 86.36% (19/22)	No significant difference
Katge <i>et al.</i> (2017) ⁷⁾	+	+ (When bleeding persisted after pressure application)	CR	12	T: 72.4% (21/29) C: 72.4% (21/29)	T: 100% (21/21) C: 100% (21/21)	No significant difference
Suhag <i>et al.</i> (2019) ⁴⁾	+	+	CR	12	T: 84.4% (27/32) C: 90.6% (29/32)	T: 93% (25/27) C: 69% (20/29)	Significant difference

CH: Calcium hydroxide; MTA: Mineral Trioxide Aggregate; AM: Amalgam; CR: Composite resin; SSC: Stainless steel crown

RESULTS

Literature identification

A flowchart summarizing the screening process is presented in Fig. 1. The electronic search retrieved 630 articles; 15 additional articles were found by the hand search. After the first screening, 271 articles were excluded because they were duplicates, reviews or published in a language other than English; 374 articles were assessed for eligibility. After the full-text evaluation, 367 articles which did not match the eligibility criteria were excluded, and 7 articles were included in this study²⁻⁸⁾.

Characteristics of the included studies

The characteristics of the included studies are presented in Table 4. Four RCTs compared CS with CH and four RCTs compared Biodentine with MTA. In these included studies, clinical success of DPC was defined as a tooth with normal response to pulp sensitivity tests, no pain, no other clinical symptoms, and no radiographic signs of root resorption and apical periodontitis.

The risk of bias in the included studies is summarized in Table 5. All included studies were judged at high risk of bias.

Fig. 1 Flowchart for the meta-analyses.

Table 5 Risk of bias of the included studies

Author (year) Ref.)	Random sequence generation	Allocation concealment	Blinding of			Selective reporting	Incomplete outcome data	Other bias	Overall
			patients	operators	outcome assessment				
Awawdeh <i>et al.</i> (2018) ²⁾	Low (coin toss)	Unclear	Low	Unclear	Low	Low	Low	Low	High
Kundzina <i>et al.</i> (2017) ⁸⁾	Low (Envelop method)	Low (Central randomization)	Low	High	Low	Low	Low	Low	High
Hilton <i>et al.</i> (2013) ⁶⁾	Low (R 2.15) (Randomization was done by practice)	Low (Central randomization)	Unclear	High	High (Operator assessed radiograph)	Low	Low	Low	High
Parinyaprom <i>et al.</i> (2017) ⁵⁾	Low (Randomization number table)	Unclear	Low	High	Low	Low	Low	Low	High
Brizuela <i>et al.</i> (2017) ³⁾	Low (Excel table)	Unclear	Unclear	High	Unclear	Low	High (Missing data can influence the result)	Low	High
Katge <i>et al.</i> (2017) ⁷⁾	Unclear	Unclear	Low	High	Unclear	Low	Low	Low	High
Suhag <i>et al.</i> (2019) ⁴⁾	Low (Envelop method)	Low (Independent research associate)	Low	High	Low	Low	Low	Low	High

Low: Low risk of bias; Unclear: Unclear risk of bias; High: High risk of bias.

CS versus CH

Four RCTs comparing CS with CH presented in Table 6 were scrutinized in the meta-analysis^{3,4,6,8}. White ProRoot MTA was used in 3 RCTs; meanwhile, ProRoot MTA and Biodentine were used in 1 RCT. CH powder (Hertz Pharmaceutical, Santiago, Chile; Prevest DenPro, Jammu, India) and Dycal (Dentsply, Milford, DE, USA) was used in 2 RCTs; meanwhile, Life (Kerr, Orange, CA, USA) was used in 1 RCT. The result is presented in Fig. 2. According to the Cochrane Q test and the I^2 statistic, the results showed moderate

heterogeneity ($df=3$; $p=0.17$; $I^2=40\%$). The total number of positive events for CS was 253 of 288 DPC treatments, whereas 189 of 260 were recorded for CH. The RR was 1.20 (95% CI, 1.06 to 1.36; $p=0.005$).

Biodentine versus MTA

Four RCTs comparing Biodentine with MTA presented in Table 7 were scrutinized in the meta-analysis^{2,3,5,7}. MTA-Angelus was used in 2 RCTs; meanwhile, WMTA and ProRoot MTA were used in 1 RCT. The result is presented in Fig. 3. According to the Cochrane Q test

Table 6 Summary of the included studies comparing CS with CH

Author (Year) ^{Ref.)}	CH (n/N)		CS (n/N)	
Brizuela <i>et al.</i> (2017) ³⁾	Powder (19/22)		Biodentine (25/25), WMTA (19/22)	
Hilton 2013	Life (132/175)		ProRoot MTA (158/183)	
Kundzina <i>et al.</i> (2017) ⁸⁾	Dycal (18/34)		WMTA (26/31)	
Suhag <i>et al.</i> (2019) ⁴⁾	Powder (20/29)		WMTA (25/27)	

CH: Calcium hydroxide; CS: Calcium silicate-based cement; WMTA: white ProRoot MTA

Fig. 2 Forest plot comparing CS with CH in terms of effectiveness of a DPC material.

Table 7 Summary of the included studies comparing Biodentine with MTA.

Author (Year) ^{Ref.)}	MTA (n/N)		Biodentine (n/N)	
Brizuela <i>et al.</i> (2017) ³⁾	WMTA (19/22)		Biodentine (25/25)	
Katge <i>et al.</i> (2017) ⁷⁾	MTA angelus (21/21)		Biodentine (21/21)	
Parinyaprom <i>et al.</i> (2017) ⁵⁾	ProRoot MTA (25/27)		Biodentine (27/28)	
Awawdeh <i>et al.</i> (2018) ²⁾	MTA angelus (5/5)		Biodentine (9/10)	

MTA: Mineral Trioxide Aggregate; WMTA: white ProRoot MTA

Fig. 3 Forest plot comparing Biodentine with MTA in terms of effectiveness of a DPC material.

Fig. 4 Funnel plot of meta-analysis comparing CS with CH (a), and Biodentine with MTA (b).

and the I^2 statistic, the results showed no heterogeneity ($df=2.71$; $p=0.44$; $I^2=0\%$). The total number of positive events for Biodentine was 82 of 84 DPC treatments; whereas, 70 of 75 were recorded for MTA. The RR was 1.03 (95% CI, 0.96 to 1.10; $p=0.40$).

Publication bias assessment

Publication bias in meta-analyses were assessed by visual inspection of funnel plots shown in Fig. 4. Statistical analyses were not performed because the number of RCTs was small. Asymmetry was not clearly observed in both funnel plots.

DISCUSSION

This study has some limitations. First, there is a risk of selection bias because only studies in English were included. Second, blinding of operators was impossible because of different clinical handling; therefore, the risk of bias in this domain is unavoidable. Third, only histological analysis can evaluate the true condition of the dental pulp tissue after DPC⁹; however, the follow-up period of studies in which histological evaluations were performed were short-term, and it is impossible to guarantee the long-term prognosis of a DPC material.

Clinical and methodological heterogeneities of both analyses were not low because of various characteristics and designs of included studies; therefore, statistical heterogeneity was analyzed to know whether it is possible to integrate studies through meta-analyses. The heterogeneity analyses using RevMan 5 indicated that the statistical heterogeneities of both analyses were not serious; therefore, meta-analyses were performed with random effect model, and subgroup analysis was not performed.

Recently, some meta-analyses of studies comparing MTA with CH on DPC success rate to permanent teeth were reported^{10–12}. In 2015, Zhu *et al.* compared success rate of MTA with that of CH, and indicated that the success rate of MTA is significantly higher than that of CH (risk difference=0.1 [95% CI, 0.04 to 0.16; $p=0.002$])¹⁰.

However, this review is unsuitable for the evaluation of MTA and CH as DPC materials because it included a RCT which evaluated the effectiveness of materials for indirect pulp capping¹³. Li *et al.* compared CH with MTA on success rate, hard-tissue barrier formation and inflammatory response; and their study indicated that the success rate of MTA was significantly higher than that of CH (odds ratio=2.26 [95% CI, 1.33 to 3.85; $p=0.003$])¹¹. However, only 2 RCTs were included in this review and one of them was 3-months follow-up study. Lots of studies are performed with less than 6 months follow-up period; however, most clinicians want to know long-term effectiveness. Therefore, studies with less than 6 months follow-up period were excluded in our study. In 2018, Paula *et al.* compared MTA with CH on success rate, hard-tissue barrier formation and inflammatory response; and their study indicated that the success rate of MTA was significantly higher than that of CH (odds ratio=2.64 [95% CI, 1.60 to 4.35; $p=0.000$])¹². However, only 2 cohort studies were included and no RCT was included in this meta-analysis. As Cohort study is less convincing than RCT, only RCTs were included in our study.

This study indicates that the success rate of CS is statistically superior to that of CH ($p=0.005$); therefore, CS seems to be a more effective and predictable DPC material than CH. Furthermore, it is reported that the long-term cost-effectiveness of MTA for DPC was better than that of CH¹⁴. However, the initial treatment cost of CS is much higher than that of CH; therefore, clinicians should discuss with patients about choice of a DPC material. Meanwhile, this study also indicates that there was no significant difference between Biodentine and MTA on DPC success rate. And Biodentine is reported to promote high amount of dentine bridge formation in human teeth without any pulpal inflammation similar to white ProRoot MTA^{15,16}. However, other properties of Biodentine such as handling, setting time and tooth discoloration are superior to white ProRoot MTA¹⁷. Thus, Biodentine is likely to be more suitable for DPC than white ProRoot MTA.

CONCLUSION

CS is likely to be a more effective and predictable DPC material than CH, and Biodentine is likely to be more suitable for DPC than white ProRoot MTA. However, data used in this study are based on the included studies judged at high risk of bias, and the statistical analysis was not performed for publication bias assessment because of small number of included RCTs. Therefore, further clinical and radiographic RCTs with long-term follow-up periods are required to confirm which material is a most suitable for DPC.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest associated with this research.

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